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Response to the Mayberg and Evans “Re-analysis”

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Fred Duchardt, Esq.

Dear Mr. Duchardt:

Evans and Mayberg's re-analysis has the error that I warned against in footnote 1 of my September 28, 2007 report. As I explained in my testimony, the 36 regions of interest (ROIs) used in the analysis of both the normative sample and of Ms. Montgomery are merely “punch biopsies” and do not represent a comprehensive sample of brain tissue. There are several other ROIs that we obtain routinely but are not included for a variety of reasons, mainly related to relevance to behavior and reliability of region placement. Averaging 36 regions of differing sizes and tissue mixtures makes no methodological sense. Certainly it does not represent gray matter (GM) metabolism, as Evans and Mayberg erroneously state in their “re-analysis” report. Indeed, two of the regions (anterior and posterior corpus callosum) are very large and purely white matter, while others contain mixture of GM and WM and yet others are pure GM. The average of 36 heterogeneously sized and composed regions is plainly meaningless and should not be used as the denominator in calculating region to whole-brain (R/WB) ratios.

The various graphs prepared by Drs. Evans and Mayberg nicely illustrate why it is so undesirable to use the average of the 36 regions (or 35 regions they used in the previous re-analysis) to normalize the data. This denominator for the R/WB ratio is unstable, depending entirely on the specific regions selected for inclusion. Contrary to their statement in their previous report, it does make a difference whether you include 35 or 36 regions, and the values will change further if we base them on averages of 34 or 33 regions. This is why we use the global volume whole-brain values in the denominator. This global value is highly stable and includes all tissue types. This is the value we used for normalization of both the sample of healthy women and of Ms. Montgomery and, when this is done, Ms. Montgomery has abnormal elevations as shown in my September 28 Figure 1.

The values I showed to the court were provided to me by the PET Center and were designed and calculated with the help of professional biostatisticians working with chemists, physicists and other experts. These procedures for calculating R/WB values are used routinely in all PET Centers that I am familiar with. Metabolic rates in

physiologic units (e.g., ml/100g/min) can be used when available, otherwise counts-per-pixel (cpp) are used. In our experience these two methods end up with very similar values (which is what I showed in Figure 1 of my September 28, 2007 report.) But the denominator for R/WB ratios has to be the volume average for the whole brain, NOT the unweighted average of a selected number of ROIs. Their ability to “reproduce” values very similar to mine in the control group, when they used the wrong method of averaging 35 or 36 ROIs, merely reflects the fact that in healthy people, by and large, such variations in calculating R/WB ratios produce negligible differences in the resulting values. But to use the same erroneous method for a patient who has increased metabolism in a significant number of ROIs is plainly misguided and artificially makes her values look more normal than she is because her abnormally high values disproportionately and spuriously inflate the inappropriate denominator.

To clarify the issue, may I recapitulate the history of this debate. In my original report I showed Ms. Montgomery’s values and the values of the control sample calculated in EXACTLY the same way: The counts-per-pixel (cpp) values for each ROI were divided by the same value (cpp) for the whole-brain. These were the values that were supplied to me by our PET Center for the healthy control sample and for Ms. Montgomery. When Evans and Mayberg asked for the metabolic rates of all individual subjects in the control sample, I re-calculated the R/WB values based on these metabolic rates, which were in physiologic units (ml/100g of tissue/minute) rather than the cpp values. Consistent with our experience, the values calculated that way are very similar to my original values because the normalization process overshadows deviations from linearity that may characterize the relation between count rates and metabolic rates. With that re-calculation we again found that Ms. Montgomery has abnormally high values in 17 regions, although a slight increase in standard deviations has placed 5 regions that were originally on the significant side of a threshold now within the normal range. Note that the data I presented in my original report (Figure 4) is the right data because it shows the values for Ms. Montgomery and the control females calculated identically (i.e., using cpp).

As you know, our PET Center is still working on producing the original count-rate values that were used by the PET Center for calculating the R/WB values shown in Figure 4 of my first report (at some point after they supplied me these values back in ~1993 they have archived the original raw numbers, which now have to be retrieved from a mothballed computer and old storage media). Once we have these numbers, they should reproduce the data shown in Figure 4 of my original report (i.e., calculated based on cpp for all ROIs and the whole-brain).

I hope this clarifies the confusion and will be happy to explain any remaining ambiguity as to what we did, how it was done, and why we have done it right. Let me know if you have any additional questions.

Sincerely,

Ruben C. Gur, Ph.D.